

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
7 February 2002 (07.02.2002)

PCT

(10) International Publication Number
WO 02/09671 A2

(51) International Patent Classification⁷: **A61K 9/107**

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(21) International Application Number: PCT/US01/24167

(22) International Filing Date: 31 July 2001 (31.07.2001)

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(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
09/630,237 1 August 2000 (01.08.2000) US

(81) Designated States (*national*): AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

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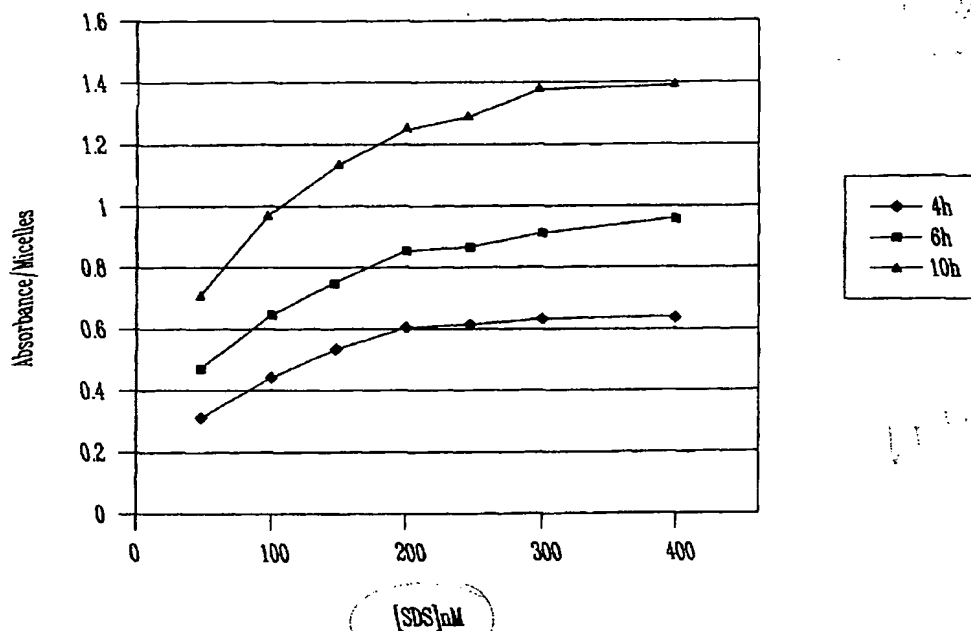
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(84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: NOVEL MICROEMULSION AND MICELLE SYSTEMS FOR SOLUBILIZING DRUGS



(57) Abstract: A microemulsion delivery system for water insoluble or sparingly water soluble drugs that comprise a long polymer chain surfactant component and a short fatty acid surfactant component, with the amount of each being selected to provide stable microemulsion or micellar systems.

TITLE: NOVEL MICROEMULSION AND MICELLE SYSTEMS FOR
SOLUBILIZING DRUGS

FIELD OF THE INVENTION

5 This invention relates to compositions and a method for making
microemulsion delivery systems for water insoluble or sparingly soluble drugs.

BACKGROUND OF THE INVENTION

Dissolving water insoluble agents into aqueous solutions appropriate for
10 human use (e.g., oral, topical application, intravenous injection, intramuscular
injection, subcutaneous injection) represents a major technological hurdle for
pharmaceutical delivery systems. Previous attempts have resulted in a
number of serious side effects caused not by the drugs, but by the carrier
agents used to dissolve the drug. These complications include significant
1) 15 hypotension during intravenous injection (e.g., amiodarone), painful injection (2)
2 with subsequent phlebitis (e.g., valium), anaphylaxis (e.g., propofol in
3 Cremaphor), postoperative infections (e.g., propofol in Intralipid), and others.
4 Clearly, an approach aimed at improving the solubilization of these drugs and
avoiding the complications of solubilizing agents would enhance the quality of
20 health care to patients. For many drugs, a major technological barrier for
their routine clinical use is very poor solubility in the aqueous phase. For such
drugs, oil/water macroemulsions have been commonly used in the
pharmaceutical industry to "dissolve" a drug to its desired concentration. For
example, the anesthetic propofol is supplied to the health care industry as
25 Baxter PPI propofol (Gensia Sicor, Inc.) or Diprivan (AstraZeneca
Pharmaceuticals, Inc.), as a macroemulsion of propofol in soybean oil (100
mg/mL), glycerol (22.5 mg/mL), egg lecithin (12 mg/mL), and disodium edetate
(0.005%) or metabisulfite; with sodium hydroxide to adjust pH to 7.0-8.5.
However, the stability of such macroemulsions is relatively poor, and the oil
30 and water components separate into distinct phases over time. In addition,
the droplet size of the macroemulsion increases with time. Macroemulsions

are defined as formed by high shear mixing and normally having particles of 1 micron to 10 microns in size.

In contrast to macroemulsion systems, microemulsion systems consisting of oil, water, and appropriate emulsifiers can form spontaneously and are therefore thermodynamically stable. For this reason, microemulsion systems theoretically have an infinite shelf life under normal conditions in contrast to the limited life of macroemulsions (e.g., two years for Baxter PPI propofol). In addition, the size of the droplets in such microemulsions remains constant and ranges from 100-1000 angstroms (10-100 nm), and has very low oil/water interfacial tension. Because the droplet size is less than 25% of the wavelength of visible light, microemulsions are transparent. Three distinct microemulsion solubilization systems that can be used for drugs are as follows:

1. oil in water microemulsions wherein oil droplets are dispersed in the continuous aqueous phase;
2. water in oil microemulsions wherein water droplets are dispersed in the continuous oil phase;
3. bi-continuous microemulsions wherein microdomains of oil and water are interdispersed within the system. In all three types of microemulsions, the interface is stabilized by an appropriate combination of surfactants and/or co-surfactants.

It can be seen from the above description that there is a real and continuing need for the development of new and effective drug delivery systems for water insoluble or sparingly soluble drugs. One such approach might be pharmaceutical microemulsions. However, one must choose materials that are biocompatible, non-toxic, clinically acceptable, and use emulsifiers in an appropriate concentration range, and form stable microemulsions. This invention has as its objective the formation of safe and effective pharmaceutical microemulsion delivery systems.

The delivery system described herein has been found particularly useful for propofol, but is not exclusively limited thereto. It is presented here as an example of a state of the art drug, normally poorly soluble in its present

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 shows release of active drug from microemulsions or micelles to Heptane phase.

Figure 2 shows similar experimental results.

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SUMMARY OF THE INVENTION

A microemulsion delivery system for normally water insoluble or sparingly soluble drugs, such as propofol. The drug is microemulsified with an emulsifier combination of a long chain polymer surfactant component and a short chain fatty acid surfactant component. These are selected to reduce surface tension to absorption between the two phases to thereby allow the formation of thermodynamically stable microemulsions or micelles. The system is particularly useful for propofol, but is not limited to propofol.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Microemulsion drug delivery systems of this invention are hereinafter described in conjunction with microemulsions with the pharmaceutically active anesthetic propofol. However, it should be understood that the use of propofol as the active water insoluble or sparingly soluble drug in the description is exemplary only of the generally described class of normally poorly water soluble drugs. Microemulsion systems of the present invention, particularly oil and water, can be used to dissolve substantial concentrations of oil-soluble drugs such as propofol, and they can thereafter be injected intravenously into human patients or animals with less, or even without pain caused by the delivery system.

Many water soluble drugs such as cyclosporine, insulin, and others can be dissolved in water-in-oil microemulsions and can be taken orally (e.g., gelatin capsule) or injected. These microemulsions spread over the intestinal surface wherein nanometer-sized water droplets with drugs dissolved therein permeate and diffuse across the intestinal brush border. The delivery of various drugs (i.e., oil-soluble, water-soluble, and interphase soluble drugs) in

patients using the previously-mentioned three types of microemulsion systems consisting of biocompatible surfactants and co-surfactants will work. Such solutions can be especially valuable to patients with abdominal disorders that inhibit absorption such as short gut syndrome and for better oral delivery of expensive drugs that are otherwise poorly absorbed.

Substantially water insoluble pharmacologically active agents contemplated for use in the practice of the present invention include pharmaceutically active agents, not limited in class, except to say they are normally difficultly soluble in aqueous systems. Examples of pharmaceutically active drug agents include: analgesics/antipyretics (e.g., aspirin, acetaminophen, ibuprofen, naproxen sodium, buprenorphine hydrochloride, propoxyphene hydrochloride, propoxyphene napsylate, meperidine hydrochloride, hydromorphone hydrochloride, morphine sulfate, oxycodone hydrochloride, codeine phosphate, dihydrocodeine bitartrate, pentazocine hydrochloride, hydrocodone bitartrate, levorphanol tartrate, diflunisal, trolamine salicylate, nalbuphine hydrochloride, mefenamic acid, butorphanol tartrate, choline salicylate, butalbital, phenyltoloxamine citrate, diphenhydramine citrate, methotrimeprazine, cinnamedrine hydrochloride, meprobamate, and the like); anesthetics (e.g., halothane, isoflurane, methoxyflurane, propofol, thiobarbiturates and the like); antiasthmatics (e.g., Azelastine, Ketotifen, Traxanox, and the like); antibiotics (e.g., neomycin, streptomycin, chloramphenicol, cephalosporin, ampicillin, penicillin, tetracycline, and the like); antidepressants (e.g., nefopam, oxypertine, doxepin hydrochloride, amoxapine, trazodone hydrochloride, amitriptyline hydrochloride, maprotiline hydrochloride, phenelzine sulfate, desipramine hydrochloride, nortriptyline hydrochloride, tranylcypromine sulfate, fluoxetine hydrochloride, doxepin hydrochloride, imipramine hydrochloride, imipramine pamoate, nortriptyline, amitriptyline hydrochloride, isocarboxazid, desipramine hydrochloride, trimipramine maleate, protriptyline hydrochloride, and the like); antidiabetics (e.g., biguanides, hormones, sulfonylurea derivatives, and the like); antifungal agents (e.g., griseofulvin, keoconazole,

amphotericin B, Nystatin, candicidin, and the like); antihypertensive agents (e.g., propranolol, propafenone, oxyprenolol, nifedipine, reserpine, trimethaphan camsylate, phenoxybenzamine hydrochloride, pargyline hydrochloride, deserpidine, diazoxide, guanethidine monosulfate, minoxidil, rescinamine, sodium nitroprusside, rauwolfia serpentina, alseroxylon, phentolamine mesylate, reserpine, and the like); anti-inflammatories (e.g., (non-steroidal) indomethacin, naproxen, ibuprofen, ramifenazone, piroxicam, (steroidal) cortisone, dexamethasone, fluazacort, hydrocortisone, prednisolone, prednisone, and the like); antineoplastics (e.g., adriamycin, cyclophosphamide, actinomycin, bleomycin, duanorubicin, doxorubicin, epirubicin, mitomycin, methotrexate, fluorouracil, carboplatin, carmustine (BCNU), methyl-CCNU, cisplatin, etoposide, interferons, camptothecin and derivatives thereof, phenesterine, taxol and derivatives thereof, taxotere and derivatives thereof, vinblastine, vincristine, tamoxifen, etoposide, piposulfan, and the like); antianxiety agents (e.g., lorazepam, buspirone hydrochloride, prazepam, chlordiazepoxide hydrochloride, oxazepam, clorazepate dipotassium, diazepam, hydroxyzine pamoate, hydroxyzine hydrochloride, alprazolam, droperidol, halazepam, chlormezanone, dantrolene, and the like); immunosuppressive agents (e.g., cyclosporine, azathioprine, mizoribine, FK506 (tacrolimus), and the like); antimigraine agents (e.g., ergotamine tartrate, propranolol hydrochloride, isometheptene mucate, dichloralphenazone, and the like); sedatives/hypnotics (e.g., barbiturates (e.g., pentobarbital, pentobarbital sodium, secobarbital sodium), benzodiazepines (e.g., flurazepam hydrochloride, triazolam, tomazepam, midazolam hydrochloride, and the like); antianginal agents (e.g., beta-adrenergic blockers, calcium channel blockers (e.g., nifedipine, diltiazem hydrochloride, and the like), nitrates (e.g., nitroglycerin, isosorbide dinitrate, pentaerythritol tetranitrate, erythrityl tetranitrate, and the like)); antipsychotic agents (e.g., haloperidol, loxapine succinate, loxapine hydrochloride, thioridazine, thioridazine hydrochloride, thiothixene, fluphenazine hydrochloride, fluphenazine decanoate, fluphenazine enanthate, trifluoperazine hydrochloride, chlorpromazine hydrochloride, perphenazine,

lithium citrate, prochlorperazine, and the like); antimanic agents (e.g., lithium carbonate); antiarrhythmics (e.g., amiodarone, related derivatives of amiodarone, bretylium tosylate, esmolol hydrochloride, verapamil hydrochloride, encainide hydrochloride, digoxin, digitoxin, mexiletine hydrochloride, disopyramide phosphate, procainamide hydrochloride, quinidine sulfate, quinidine gluconate, quinidine polygalacturonate, flecainide acetate, tocainide hydrochloride, lidocaine hydrochloride, and the like); antiarthritic agents (e.g., phenylbutazone, sulindac, penicillamine, salsalate, piroxicam, azathioprine, indomethacin, meclofenamate sodium, gold sodium thiomalate, ketoprofen, auranofin, aurothioglucose, tolmetin sodium, and the like); antigout agents (e.g., colchicine, allopurinol, and the like); anticoagulants (e.g., heparin, heparin sodium, warfarin sodium, and the like); thrombolytic agents (e.g., urokinase, streptokinase, alteplase, and the like); antifibrinolytic agents (e.g., aminocaproic acid); hemorheologic agents (e.g., pentoxifylline); antiplatelet agents (e.g., aspirin, empirin, ascriptin, and the like); anticonvulsants (e.g., valproic acid, divalproate sodium, phenytoin, phenytoin sodium, clonazepam, primidone, phenobarbital, phenobarbital sodium, carbamazepine, amobarbital sodium, methsuximide, metharbital, mephobarbital, mephentyoin, phensuximide, paramethadione, ethotoin, phenacemide, secobarbital sodium, clorazepate dipotassium, trimethadione, and the like); antiparkinson agents (e.g., ethosuximide, and the like); antihistamines/antipruritics (e.g., hydroxyzine hydrochloride, diphenhydramine hydrochloride, chlorpheniramine maleate, brompheniramine maleate, cyproheptadine hydrochloride, terfenadine, clemastine fumarate, triprolidine hydrochloride, carbinoxamine maleate, diphenylpyraline hydrochloride, phenindamine tartrate, azatadine maleate, tripeleennamine hydrochloride, dexchlorpheniramine maleate, methdilazine hydrochloride, trimiprazine tartrate and the like); agents useful for calcium regulation (e.g., calcitonin, parathyroid hormone, and the like); antibacterial agents (e.g., amikacin sulfate, aztreonam, chloramphenicol, chloramphenicol palmitate, chloramphenicol sodium succinate, ciprofloxacin hydrochloride, clindamycin

hydrochloride, clindamycin palmitate, clindamycin phosphate, metronidazole, metronidazole hydrochloride, gentamicin sulfate, lincomycin hydrochloride, tobramycin sulfate, vancomycin hydrochloride, polymyxin B sulfate, colistimethate sodium, colistin sulfate, and the like); antiviral agents (e.g.,
5 interferon gamma, zidovudine, amantadine hydrochloride, ribavirin, acyclovir, and the like); antimicrobials (e.g., cephalosporins (e.g., cefazolin sodium, cephadrine, cefaclor, cephapirin sodium, ceftizoxime sodium, cefoperazone sodium, cefotetan disodium, cefutaxime azotil, cefotaxime sodium, cefadroxil monohydrate, ceftazidime, cephalixin, cephalothin sodium, cephalixin
10 hydrochloride monohydrate, cefamandole nafate, cefoxitin sodium, cefonicid sodium, ceforanide, ceftriaxone sodium, ceftazidime, cefadroxil, cephadrine, cefuroxime sodium, and the like), prythronycins, penicillins (e.g., ampicillin, amoxicillin, penicillin G benzathine, cyclacillin, ampicillin sodium, penicillin G potassium, penicillin V potassium, piperacillin sodium, oxacillin sodium,
15 bacampicillin hydrochloride, cloxacillin sodium, ticarcillin disodium, azlocillin sodium, carbenicillin indanyl sodium, penicillin G potassium, penicillin G procaine, methicillin sodium, nafcillin sodium, and the like), erythromycins (e.g., erythromycin ethylsuccinate, erythromycin, erythromycin estolate, erythromycin lactobionate, erythromycin siearate, erythromycin
20 ethylsuccinate, and the like), tetracyclines (e.g., tetracycline hydrochloride, doxycycline hyclate, minocycline hydrochloride, and the like), and the like); anti-infectives (e.g., GM-CSF); bronchodilators (e.g., sympathomimetics (e.g., epinephrine hydrochloride, metaproterenol sulfate, terbutaline sulfate, isoetharine, isoetharine mesylate, isoetharine hydrochloride, albuterol sulfate,
25 albuterol, bitolterol, mesylate isoproterenol hydrochloride, terbutaline sulfate, epinephrine bitartrate, metaproterenol sulfate, epinephrine, epinephrine bitartrate), anticholinergic agents (e.g., ipratropium bromide), xanthines (e.g., aminophylline, dyphylline, metaproterenol sulfate, aminophylline), mast cell stabilizers (e.g., cromolyn sodium), inhalant corticosteroids (e.g.,
30 flurisolidebeclomethasone dipropionate, beclomethasone dipropionate monohydrate), salbutamol, beclomethasone dipropionate (BDP), ipratropium

bromide, budesonide, ketotifen, salmeterol, xinafoate, terbutaline sulfate, triamcinolone, theophylline, nedocromil sodium, metaproterenol sulfate, albuterol, flunisolide, and the like); hormones (e.g., androgens (e.g., danazol, testosterone cypionate, fluoxymesterone, ethyltestosterone, testosterone enanthate, methyltestosterone, fluoxymesterone, testosterone cypionate), estrogens (e.g., estradiol, estropipate, conjugated estrogens), progestins (e.g., methoxyprogesterone acetate, norethindrone acetate), corticosteroids (e.g., triamcinolone, betamethasone, betamethasone sodium phosphate, dexamethasone, dexamethasone sodium phosphate, dexamethasone acetate, prednisone, methylprednisolone acetate suspension, triamcinolone acetonide, methylprednisolone, prednisolone sodium phosphate methylprednisolone sodium succinate, hydrocortisone sodium succinate, methylprednisolone sodium succinate, triamcinolone hexacetonide, hydrocortisone, hydrocortisone cypionate, prednisolone, fluorocortisone acetate, paramethasone acetate, prednisolone tebutate, prednisolone acetate, prednisolone sodium phosphate, hydrocortisone sodium succinate, and the like), thyroid hormones (e.g., levothyroxine sodium) and the like), and the like; hypoglycemic agents (e.g., human insulin, purified beef insulin, purified pork insulin, glyburide, chlorpropamide, glipizide, tolbutamide, tolazamide, and the like); hypolipidemic agents (e.g., clofibrate, dextrothyroxine sodium, probucol, lovastatin, niacin, and the like); proteins (e.g., DNase, alginase, superoxide dismutase, lipase, and the like); nucleic acids (e.g., sense or anti-sense nucleic acids encoding any therapeutically useful protein, including any of the proteins described herein, and the like); agents useful for erythropoiesis stimulation (e.g., erythropoietin); antiulcer/antireflux agents (e.g., famotidine, cimetidine, ranitidine hydrochloride, and the like); antinauseants/antiemetics (e.g., meclizine hydrochloride, nabilone, prochlorperazine, dimenhydrinate, promethazine hydrochloride, thiethylperazine, scopolamine, and the like); oil-soluble vitamins (e.g., vitamins A, D, E, K, and the like); as well as other drugs such as mitotane, visadine, halonitrosoureas, anthrocyclines, ellipticine, and the like.

As well, the microemulsion systems of the present invention may be used in brain chemotherapy and gene chemotherapy, since the nature of the surface of virus particles is an important determinant of the transfer rate of viruses across the blood/brain barrier or into another protected compartment
5 (e.g., intraocular cerebrospinal fluid).

Likewise, many chemotherapeutic agents dissolved in an oil in water microemulsion might be more readily delivered to a tumor site in the brain. For example, pediatric patients with brain tumors may frequently require general anesthesia so that chemotherapeutic agents can be safely injected into
10 the cerebrospinal fluid by puncture of the lumbar cistern. Use of microemulsions to target brain tumors might obviate the need for anesthesia and/or lumbar puncture in adult and pediatric patients.

The solubility of nonpolar drugs can be significantly increased if dissolved in mixed solvents such as water and alcohol or propylene glycol by
15 influencing the hydrophobic forces existing in the system. This approach will also be compared with microemulsion and selective micelle release systems. The mixed solvent system may be the simplest method to solve problems of drug solubilization.

In preparation of the pharmaceutically active drug such as propofol
20 useful in highly bioavailable form in accordance with the present invention, the first step is to select the normally difficultly soluble drug, such as propofol, which is similar to an oil. In order to make a homogeneous microemulsion of the pharmaceutically active component such as propofol, one needs to mix it with the appropriate emulsifier combination for formation of the
25 microemulsion.

Surprisingly, it has been found that in accordance with the present invention, the appropriate combination of surfactants is the combination of a long chain polymer surfactant component such as a poloxamer with a short chain fatty acid surfactant component. The ratio of long chain polymer
30 surfactant to short chain fatty acid surfactant should be from 10 to 100, preferably from 25 to 80 (wt./wt.).

O/w

Suitable long chain surfactants can be selected from the group known as organic or inorganic surfactant pharmaceutical excipients. Preferred surfactants include nonionic and anionic surfactants.

Representative examples of long chain or high molecular weight (>1000) surfactants include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium, carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthalate, microcrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidene (PVP). The low molecular weight (<1000) include stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate, cetostearyl alcohol, cetomacrogol emulsifying wax, and sorbitan esters. Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986.

Particularly preferred long chain surfactants include polyvinylpyrrolidone, tyloxapol, poloxamers such as Pluronic F68, F77, and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyxamines such as Tetronic 908 (also known as Poloxamine 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, available from BASF, dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanamid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 20 and Tween 80, which are polyoxyethylene

sorbitan fatty acid esters, available from ICI Specialty Chemicals; Carbowax 3550 and 934, which are polyethylene glycols available from Union Carbide; Crodesta F-110, which is a mixture of sucrose stearate and sucrose distearate, available from Croda Inc., Crodesta SL-40, which is available from Croda, Inc.,
5 and SA90HCO, which is C.sub.18 H.sub.37 -

CH.sub.2(CON(CH.sub.3)CH.sub.2 (CHOH).sub.4 CH.sub.2 OH).sub.2.

Surface modifiers which have been found to be particularly useful include Tetronic 908, the Tweens, Pluronic F-68 and polyvinylpyrrolidone. Other useful surface modifiers include: decanoyl-N-methylglucamide; n-decyl.beta-D-glucopyranoside; n-decyl.beta-D-maltopyranoside; n-dodecyl.beta-D-glucopyranoside; n-dodecyl.beta.-D-maltoside; heptanoyl-N-methylglucamide; n-heptyl-.beta.-D-glucopyranoside; n-heptyl.beta.-D-thioglucoside; n-hexyl.beta.-D-glucopyranoside; nonanoyl-N-methylglucamide; n-nonyl.beta.-D-glucopyranoside; octanoyl-N-methylglucamide; n-octyl.beta.-D-glucopyranoside; octyl.beta.-D-thioglucopyranoside; and the like.
15

Another useful long chain surfactant is tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type; also known as superinone or triton). This surfactant is commercially available and/or can be prepared by techniques known in the art.

20 Another preferred surfactant p-isononylphenoxypoly (glycidol) also known as Olin-10G or Surfactant 10-G, is commercially available as 10G from Olin Chemicals, Stamford, Conn.

One preferred long chain surfactant is a block copolymer linked to at least one anionic group. The polymers contain at least one, and preferably
25 two, three, four or more anionic groups per molecule. Preferred anionic groups include sulfate, sulfonate, phosphonate, phosphate and carboxylate groups. The anionic groups are covalently attached to the nonionic block copolymer. The nonionic sulfated polymeric surfactant has a molecular weight of 1,000-50,000, preferably 2,000-40,000, and more preferably 3,000-30,000. In
30 preferred embodiments, the polymer comprises at least about 50%, and more preferably, at least about 60% by weight of hydrophilic units, e.g., alkylene

oxide units. The reason for this is that the presence of a major weight proportion of hydrophilic units confers aqueous solubility to the polymer.

A preferred class of block copolymers useful as surface modifiers herein includes block copolymers of ethylene oxide and propylene oxide. These block
5 copolymers are commercially available as Pluronics. Specific examples of the block copolymers include F68, F77, F108 and F127.

Another preferred class of block copolymers useful herein include tetrafunctional block copolymers derived from sequential addition of ethylene oxide and propylene oxide to ethylene diamine. These polymers, in an
10 unsulfated form, are commercially available as Tetronics.

To summarize, the long chain surfactant is preferably a block copolymer which is a poloxamer which is a copolymer of ethylene oxide and propylene oxide. These copolymers are commercially available as Pluronics®.

The second component of the co-surfactant or emulsifier combination is
15 a short chain fatty acid component. By short chain is meant C₈ to C₁₆ chain length, preferably, C₈ to C₁₂. One preferred co-emulsifier with especially good results is sodium laurate.

The advantages of this combination system are that one can solubilize a broad range of concentrations of active drugs and optimize the exact
20 composition of the microemulsion components. For example, with respect to propofol, high concentrations can be achieved if desired by using higher concentrations of the co-emulsifiers. Concentrations of propofol used by healthcare providers (i.e., 1% concentrate, 10 mg/mL) can be very easily achieved in the present system shown by Tables 1, 2, 3 and 4 with respect to
25 the examples below. These are all clear solutions, colorless, thermodynamically stable over time (currently these have been demonstrated for stability up to at least 16 months), and do not support bacterial growth.

In addition to microemulsions, one can design the interface of such nanometer-sized droplets so that droplet stability and lifespan in humans can
30 be selectively designed to last from a few milliseconds to minutes, or even to hours. We believe that the interfacial rigidity of the microemulsion droplets

spans of several hours. Because the therapeutic index for cardiotoxic effects of lidocaine is much greater than that for bupivacaine, use of tailored micelles would significantly enhance patient safety. (Therapeutic index is a pharmacological term regarding the margin of safety to be expected for a certain concentration of a drug to produce a desired effect [e.g., TD_{50}] compared to the concentration that causes an undesired effect [e.g., LD_{50}]). Similarly, long-lived micelles might be useful for coating drug particles or viruses for permeation through the blood/brain barrier.

The following examples are further offered to illustrate but not limit the invention. In the examples herein, propofol was used as the drug selected. Propofol was used with a microemulsion emulsifier combination of Pluronic® F77 and sodium laurate in amounts specified below. Microemulsions with the emulsifier combination saline and propofol were made. Stability and viscosity were determined, using conventional methods and tabulated in Tables 1, 2, 3 and 4 below.

TABLE 1: Formulation parameters of propofol microemulsions

Total volume = 100 ml

Sample Number	Pluronic F-77(gm)	Sodium laurate(gm)	Propofol(ml)
1A	4.0	---	---
2A	4.0	---	1.0
3A	4.0	0.05	1.0
4A	4.0	0.10	1.0
5A	4.0	0.15	1.0
1B	4.5	---	---
2B	4.5	---	1.0
3B	4.5	0.05	1.0
4B	4.5	0.10	1.0
5B	4.5	0.15	1.0

TABLE 2. The effect of temperature, and sodium laurate concentration and storage time on droplet size of propofol microemulsions.

Age	Particle Size(nm) Freshly prepared(A)		Particle Size(nm) 2 weeks later(B)		Particle Size(nm) 5 months later(C)	
	25°C	37°C	25°C	37°C	25°C	37°C
1A	---	---	---	---	---	---
2A	93.4	35.5	96.4	36.2	104.3	39.1
3A	29.8	28.1	30.9	28.7	33.5	30.1
4A	29.3	26.9	30.4	28.2	31.5	29.0
5A	25.1	24.2	25.7	25.1	25.3	25.1
1B	---	---	---	---	---	---
2B	72.1	32.8	78.7	35.8	85.6	38.3
3B	29.3	27.4	29.7	27.7	30.5	28.3
4B	26.9	25.1	27.4	25.6	27.4	25.8
5B	24.6	24.1	24.7	24.3	24.9	24.7

5

What is claimed is:

1. A microemulsion delivery system for normally difficulty soluble drugs comprising: microemulsion oil droplets of a normally difficulty soluble drug;
5 said microemulsion size droplets being emulsified with an emulsifier combination; said emulsifier combination comprising a long chain polymer surfactant component and a short chain fatty acid surfactant component, the amounts of each component being selected to provide thermodynamically stable microemulsion droplets.
- 10 2. The drug composition of claim 1 wherein the particle size of the microemulsion droplets is from 10 nm to 100 nm.
3. The delivery system of claim 2 wherein the long chain polymer
15 surfactant component is selected from the group consisting of polyoxyethylene alkyl ethers, polyoxyethylene glycols, polyvinylpyrrolidone, polyvinylalcohol, tyloxapol, and poloxamer.
4. The delivery system of claim 3 wherein the long chain polymer
20 surfactant component is a poloxamer.
5. The delivery system of claim 2 wherein the short chain fatty acid component is a C₈ to C₁₆ component.
- 25 6. The delivery system of claim 5 wherein the short chain fatty acid component is a C₈ to C₁₂ component.
7. The delivery system of claim 1 wherein the long chain surfactant component is a poloxamer and the fatty acid component is a laurate.

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8. The delivery system of claim 1 wherein the normally difficultly soluble drug is an oil.
9. The delivery system of claim 1 wherein the normally difficultly soluble
5 drug is a solid.
10. The delivery system of claim 1 wherein the normally difficultly soluble drug is selected from the group consisting of analgesics, anesthetics, antibiotics, antidepressants, antidiabetics, antifungals, antihypertensives,
10 anti-inflammatories, antineoplastics, immunosuppressives, sedatives, antianginals, antipsychotics, antimanics, antiarthritics, antigouts, anticoagulants, antithrombolytics, anticonvulsants, antiparkinsons, antibacterials, antivirals, and anti-infectives.
- 15 11. The delivery system of claim 10 wherein the drug is an anesthetic.
12. The delivery system, of claim 11 wherein the drug is an aryl.
13. The delivery system of claim 12 wherein the drug is propofol.
20
14. The delivery system of claim 2 wherein the ratio of long chain polymeric component to short chain fatty acid component is from 10 to 100 to 25 to 80 (wt/wt).
- 25 15. The delivery system of claim 2 wherein the long chain polymeric component has a molecular weight greater than 1000, and the short chain fatty acid component has a molecular weight less than 1000.
16. The delivery system of claim 14 wherein the amount of normally
30 difficultly soluble drug is from 0.1% to 1.0%.

17. The microemulsion of claim 1 wherein the microemulsion is selected from the group consisting of oil-in-water, water-in-oil and interphase emulsions.
- 5 18. The microemulsion of claim 1 wherein the normally difficultly soluble drug is a mixture of the base form and the salt form of the drug.
19. The microemulsion of claim 1 wherein the drug transfer rate is controlled by control of the character and nature of micelle formation of the
10 microemulsion.
nm.
20. A method of controlling drug delivery and transfer rate of normally difficultly soluble drugs comprising: preparing microdroplets of the normally
15 difficulty soluble drug with an emulsifier combination of a long chain polymer surfactant component, and a short chain fatty acid surfactant component, the amounts of each being selected to provide thermodynamically stable microemulsion droplets and to control delivery and transfer rate as desired.

